MAR 26 1996

Morphine Sulfate CR Tablet
200 mg
ANDA # 74-769
Reviewer: Moheb H. Makary
WP 74769SD.095

AB Generics L.P.
Norwalk, CT
Submission Date:
October 16, 1995

## Review of Bioequivalence Studies and Dissolution Data

I. Objective:

The firm submitted two bioequivalence studies to assess the bioequivalence of the AB Generics's Morphine Sulfate Controlled Release (CR) Tablets, 200 mg, to Purdue Frederick's MS Contin® Controlled Release 200 mg Tablets. Dissolution profiles comparing AB Generics's Morphine Sulfate (CR) tablets and MS Contin® tablets were submitted.

The following studies were conducted and included in the submission:

1. Study #MO93-0602
A single dose randomized four-way crossover bioequivalence study of Morphine Sulfate Controlled Release (CR) 200 mg tablets under fasting and nonfasting conditions.

2. Study #MO94-0309
A two-way crossover, multiple-dose bioequivalence study of Morphine Sulfate Controlled Release (CR) 200 mg tablets under fasting conditions.

II. Introduction:

Morphine is indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.
Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is controlled release or a conventional formulation. Because of pre-systemic elimination (i.e., metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment, and peak plasma concentrations occurring between 30 minutes to 1.5 hours. The elimination half-life of the drug is estimated to be 3-4 hours. Morphine undergoes conjugation with glucuronic acid, to form the major inactive metabolite, morphine-3-glucuronide (M-3-G), the active metabolite, morphine-6-glucuronide (M-6-G) and the inactive metabolite , morphine-3,6-diglucuronide (M3,6G). The drug is excreted in urine mainly as metabolites and free morphine accounts for less than 10% of an administered dose. About 90% of the total urinary excretion occurs within 24 hours. About 7-10% of a dose of morphine is

excreted in feces mostly via bile, and there is also some enterohepatic recycling.

Morphine Sulfate is available commercially as an oral solution, oral tablets, oral soluble tablets, oral extended-release tablets, oral film-coated, extended-release tablets, parenteral injection and rectal suppositories. Morphine Sulfate Controlled Release 200 mg Tablet (MS Contin$^{R}$) is marketed by Purdue Frederick.

III. Study #MO93-0602 For Single-Dose, Four-Way Crossover Of Morphine Sulfate Controlled Release Tablets, 200 mg, Under Fasting an Nonfasting Conditions:

The objective of the study was to compare the bioavailability of Morphine Sulfate Controlled Release (CR) tablets manufactured by AB Generics, with that of Purdue Frederick product (MS Contin$^{R}$), following an oral administration of a single 200 mg dose (1x200 mg tablet) of each product under fasting and nonfasting conditions. Morphine and its metabolite, morphine-6-glucuronide, concentrations in plasma were assayed.

| | |
|---|---|
| Clinical site: | (b)(4)(CC) |
| Analytical site: | |
| Investigators: | |
| Sponsor: | The Purdue Frederick Company, Norwalk, CT. (AB Generics is a new generic company associated with The Purdue Frederick Company) |
| Study design: | Single-dose, four-way crossover bioequivalence study, under fasting and nonfasting conditions. |
| Dose dates: | January 31, 1994 - February 21, 1994 |
| Analysis dates: | June 10, 1994 - August 2, 1994 |
| Subjects: | Twenty-eight (28) normal, adult healthy male and female subjects were accepted for entry into the clinical portion of the study. Five subjects were Hispanic and twenty-three were Caucasian. Twenty-six (26) subjects successfully completed the study. Subject #12 was discontinued prior to period II due to a positive urine screen for opioids. Subject # 16 voluntarily withdrew due to adverse experiences after the initial naltrexone administration and never received morphine. |

Inclusion criteria: Male and female subjects were between 21 to 45 years of age. All subjects were within ±10% of their ideal body weight for height and body frame as described in the Metropolitan Life Insurance Company Statistical Bulletin, 1983. Subjects were judged to be in good health following a complete physical examination, ECG and medical history within fourteen days of the start of the study. In addition, urine samples at the time of the medical examination were free of drug abuse (including marijuana). Good health was confirmed by normal findings in the following tests: biochemical profile, hematology and urinalysis. Female subjects had a negative serum pregnancy test at screening and at time of dosing. Subjects had a negative Narcan$^{R}$ challenge test.

Exclusion criteria: Consisted of adverse reactions or allergy to opioid drugs, history of alcohol or drug abuse, history of cardiovascular, neurological, neuropsychiatric, gastrointestinal, hepatic, renal, hematological and/or respiratory diseases, use of prescription medication, including vitamin and/or mineral supplements within two weeks prior to study initiation or OTC medication during the seven days preceding study initiation and throughout this study and female subjects taking systemic contraceptive agents.

Dosing regimens:

A. Reference product: MS Contin® 1x200 mg tablet (Purdue Frederick Company), lot #3GP, administered within five minutes after completion of a high fat breakfast.

B. Reference product: MS Contin® 1x200 mg tablet (Purdue Frederick Company), lot #3GP, Exp. 12/94, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.

C. Test product: Morphine Sulfate Controlled-Release 1x200 mg tablet (Purdue Frederick Company), lot #4WD, administered within five minutes after completion of a high fat breakfast.

D. Test product: Morphine Sulfate Controlled-Release 1x200 mg tablet (Purdue Frederick Company), lot #4WD, batch size (b)(4)(CC)

Tablets, Exp. 10/95, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.

Narcan® Challenge Test: Prior to dosing in period I, and after ascertainment of a (negative urine drug screen, a Narcan® (Naloxone) challenge test was administered. This test was conducted after subjects have checked into the facility 26 hours prior to test medication dosing and before receiving their first dose Trexan™ (the test should not be performed in a subject showing clinical symptoms of opioid withdrawal or in a subject whose urine contains opioids).

Trexan® Administration: After it was determined that, for each subject, both the urine drug screen and the Narcan® challenge test results were negative, 2x50 mg tablets of naltrexone HCl (Trexan™) were administered at least 24 hours prior to the scheduled time of dosing in period I. This dose of naltrexone was administered again at the time of dosing and again at 24 hours after dosing. Naltrexone is an antagonist competing for the same receptor sites as morphine and is expected to diminish the potential adverse effects of morphine, especially respiratory depression. The use of a twice a day oral dose of 50 mg of naltrexone slightly alter the absolute bioavailability of oral morphine, but do not interfere with the determination of the comparative bioavailability.

Washout period: One week

Food and fluid intake: All subjects fasted for ten hours prior to dosing. Lunch was served four hours after dosing. Dinner was served eleven hours after dosing. Water was not allowed four hours after dosing, except for the dosing water (240 mL). Subjects on regimen A and C ingested the tablet with 240 mL of water within 5 minutes after a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice).

| Treatment Group | Subject Number |
|---|---|
| A->B->C->D | 4, 7, 9, 16, 18, 23, 28 |
| B->A->D->C | 3, 8, 12, 14, 17, 21, 26 |
| C->D->A->B | 2, 5, 11, 15, 19, 22, 27 |
| D->C->B->A | 1, 6, 10, 13, 20, 24, 25 |

Treatments Codes: A=MS Contin 200 mg nonfasting
B=MS Contin 200 mg fasting
C=MS (Generics) 200 mg nonfasting
D=MS (Generics) 200 mg Fasting

Blood sample times: Pre-dose (0 hr) and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24, 30, 36 and 48 hours after dosing.

Subject welfare: Vital signs (blood pressure and pulse rate) were measured just prior to each dose (within 30 minutes) and at 2, 4, 8, 12, 24 and 48 hours post-dose.

Assay Methodology

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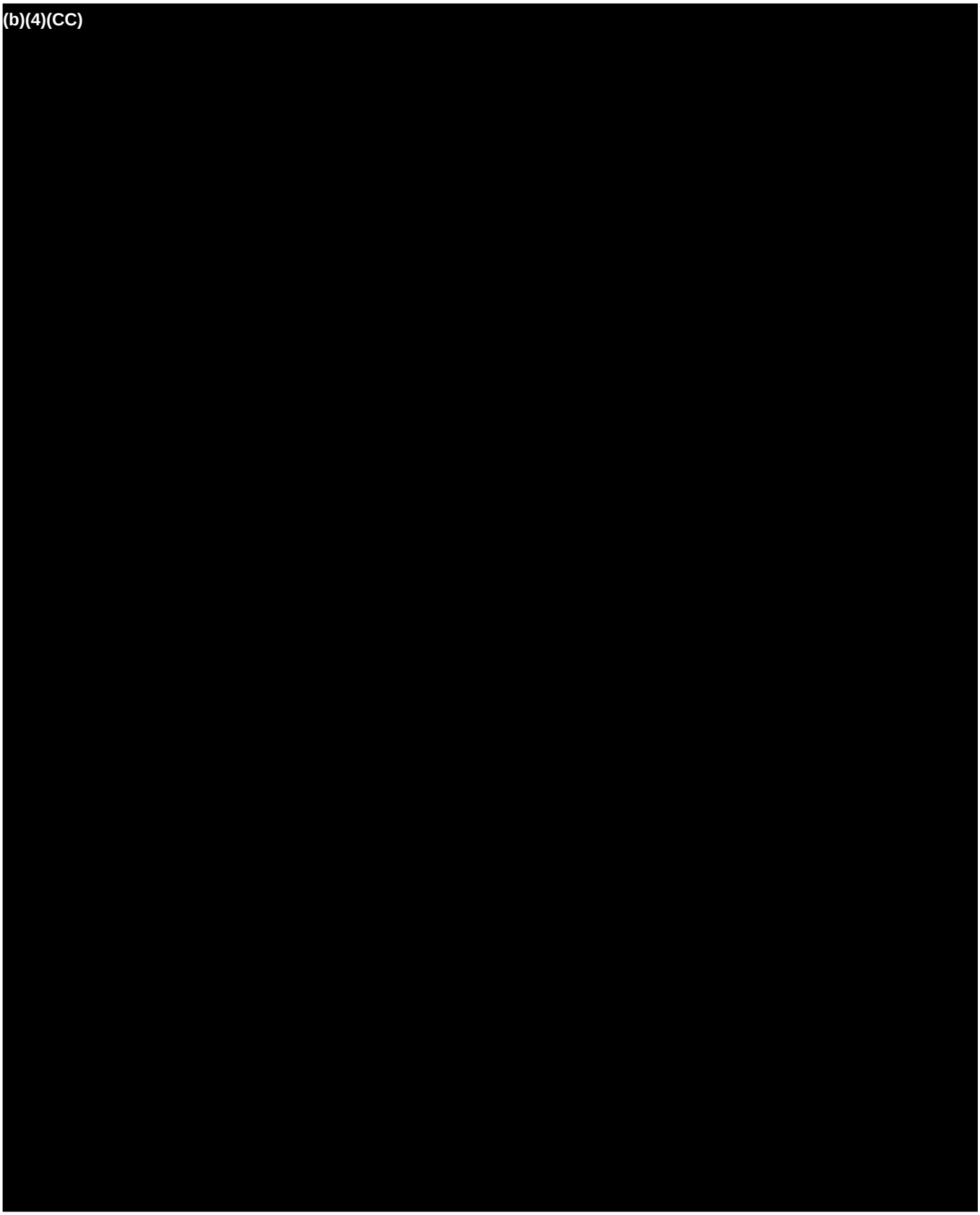

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Statistical Analysis:

Statistical analysis was performed on morphine and morphine-6-glucuronide data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval.

IV. In Vivo Results:

Twenty-eight (28) normal, healthy male and female subjects were

enrolled and 26 subjects completed all four periods of dosing. Sixteen (16) males and 12 female were selected. Two subjects did not complete the study. Subject #12 was discontinued prior to period II due to a positive urine test for opioids. The subject tested negative at screening and period I (on 1/24/94) and then received MS Contin$^{R}$ mg under fasting conditions on 1/26/94. He tested positive on 2/1/94. Subject #16, a 31 year old female, subject withdrew due to adverse experiences of lightheadedness and hot flashes after the first naltrexone administration and never received morphine. There were 11 female and 15 male subjects completing the study.

Eighty-nine (89) adverse experiences were reported during the study. Nine were considered to be of moderate severity and the remainder were considered mild. None were considered to be serious. Overall, 51 adverse experiences were considered unrelated to study drug, 16 were considered probably related and 22 were considered possibly related. The adverse experiences were those standardly reported with the use of morphine or other opioid analgesics. These included nausea, somnolence, headache, dizziness, asthenia, vasodilation, emphoria, paresthesia, vomiting and hypertonia.
The results indicate that the incidence of adverse experiences were similar between the test and reference drugs under fasting and nonfasting conditions for both male and female subjects. Except for an increased incidence of headaches and nausea in the females, there were no striking differences between the gender groups in the incidence and nature of the reports.

The plasma concentrations and pharmacokinetic parameters for Morphine and Morphine-6-Glucuronide (G-6-G) are summarized in Tables I and II.

## Table I

### Mean Plasma Morphine Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 mg Morphine Sulfate Controlled Release Tablet under Fasting and nonfasting Conditions
(N=26)

| Time hr | B Fasting Reference Lot #3GP ng/mL(CV) | D Fasting Generics-Test Lot # 4WD ng/mL(CV) | A Nonfasting Reference Lot #3GP ng/mL(CV) | C Nonfasting Generics-Test Lot #4WD ng/mL(CV) |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 0.5 | 56.1 (48.1) | 41.0 (68.8) | 34.9(109.8) | 31.0(110.2) |
| 0.75 | 70.8 (48.1) | 63.2 (81.2) | 60.5 (88.3) | 54.5(106.9) |
| 1 | 82.8 (57.9) | 78.1 (59.7) | 68.5 (71.3) | 69.9 (79.7) |
| 1.5 | 94.0 (43.4) | 86.9 (42.7) | 114.1 (69.4) | 91.2 (55.1) |
| 2 | 98.0 (53.7) | 85.2 (44.3) | 121.2 (59.2) | 118.9 (59.3) |
| 2.5 | 88.4 (50.8) | 86.7 (47.9) | 125.7 (55.4) | 116.1 (38.9) |
| 3 | 78.6 (50.3) | 81.3 (53.1) | 121.2 (45.6) | 112.0 (37.8) |
| 3.5 | 75.2 (49.4) | 81.3 (48.9) | 122.4 (41.3) | 112.8 (31.4) |
| 4 | 75.5 (54.9) | 76.7 (50.9) | 106.5 (47.1) | 114.4 (40.2) |
| 6 | 49.4 (52.0) | 53.9 (54.6) | 78.9 (46.1) | 83.8 (60.4) |
| 8 | 33.3 (42.9) | 34.4 (44.1) | 56.4 (41.5) | 64.2 (52.7) |
| 10 | 31.0 (44.4) | 30.9 (44.7) | 39.1 (48.6) | 43.8 (56.3) |
| 12 | 35.9 (32.8) | 35.7 (44.5) | 29.9 (40.3) | 31.4 (37.5) |
| 18 | 26.7 (29.8) | 27.0 (43.7) | 18.4 (43.5) | 19.2 (43.2) |
| 24 | 19.5 (42.7) | 19.1 (39.0) | 13.4 (49.8) | 14.6 (45.5) |
| 30 | 16.3 (49.7) | 14.8 (49.9) | 10.4 (43.2) | 10.8 (48.3) |
| 36 | 8.7 (60.9) | 9.6 (55.4) | 6.4 (50.5) | 5.9 (59.6) |
| 48 | 4.5 (64.6) | 6.3 (66.7) | 3.6 (79.2) | 3.9 (61.8) |

| | | | | | 90% CI |
|---|---|---|---|---|---|
| AUC(0-48) (ng.hr/mL) | 1235(34) | 1238(36) | 1290(32) | 1322(32) | |
| AUCinf (ng.hr/mL) | 1275(34) | 1293(37) | 1313(32) | 1346(32) | |
| Cmax(ng/mL) | 130.8(41) | 120.6(40) | 164.8(42) | 170.3(38) | |
| Tmax (hr) | 1.6 | 1.9 | 2.4 | 2.6 | |
| LnAUC (Fasting) | | | | | 95.0-103.9 |
| LnAUCinf (Fasting) | | | | | 95.9-104.9 |
| LnCmax (Fasting) | | | | | 81.8-105.4 |
| C/A (Nonfasting) | | | | | |
| AUC(0-48) | | | | | 1.02 |
| AUCinf | | | | | 1.03 |
| Cmax | | | | | 1.03 |

Morphine

1. For morphine, the least squares means for AUC(0-48), AUCinf and Cmax values were 0.4%, 1.6% higher and 7.9% lower, respectively, for the test product than for the reference product under fasting conditions. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The morphine plasma levels peaked at 1.5 and 2 hours for the test and reference products, respectively, following their administration under fasting conditions.

3. For AB Generics' test product, the least squares means for AUC(0-48), AUCinf and Cmax values were 2.7%, 2.8% and 3.2% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-48), AUCinf and Cmax.

4. The morphine plasma levels peaked at 2 and 2.5 hours for the test and the reference products, respectively, under nonfasting conditions.

5. For the test and reference products, the mean Cmax values after dosing with food were about 141.2% and 126.0%, respectively, of the values reported in the fasting state. Also, after feeding the Tmax was delayed about 0.8 hour relative to the fasting Tmax for both products.

4. There were no statistically significant carry-over effects for AUC(0-48), AUCinf and Cmax between the four treatments.

Table II

Mean Plasma M-6-G Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 200 mg Morphine Sulfate Controlled Release Tablet under Fasting and nonfasting Conditions
(N=26)

| Time hr | B Fasting Reference Lot #3GP ng/mL(CV) | D Fasting Generics-Test Lot # 4WD ng/mL(CV) | A Nonfasting Reference Lot #3GP ng/mL(CV) | C Nonfasting Generics-Test Lot #4WD ng/mL(CV) |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 0.5 | 23.5 (59.7) | 22.7 (76.0) | 11.1(107.1) | 12.1(142.5) |
| 0.75 | 52.8 (52.0) | 57.0 (65.5) | 31.7 (84.1) | 34.9(105.5) |
| 1 | 155.5 (50.7) | 101.1 (52.7) | 79.2 (78.3) | 80.1 (93.8) |
| 1.5 | 179.1 (43.4) | 184.8 (55.0) | 140.8 (51.2) | 147.2 (70.8) |
| 2 | 223.9 (27.7) | 243.3 (41.7) | 217.9 (57.4) | 218.8 (48.9) |
| 2.5 | 270.6 (29.2) | 271.9 (31.4) | 264.7 (53.5) | 288.4 (44.3) |
| 3 | 286.2 (39.8) | 288.4 (27.3) | 304.8 (39.2) | 339.0 (52.7) |
| 3.5 | 267.3 (34.7) | 283.8 (28.2) | 323.1 (47.1) | 317.0 (48.6) |
| 4 | 265.5 (42.1) | 273.9 (36.9) | 309.8 (39.8) | 353.7 (33.8) |
| 6 | 202.0 (54.6) | 224.7 (44.2) | 279.1 (40.6) | 297.0 (44.3) |
| 8 | 113.9 (34.2) | 139.3 (37.8) | 185.8 (44.2) | 183.3 (31.9) |
| 10 | 104.4 (46.0) | 111.2 (35.3) | 128.4 (42.7) | 136.0 (31.3) |
| 12 | 105.3 (31.5) | 108.1 (33.3) | 89.4 (34.4) | 94.6 (33.7) |
| 18 | 91.0 (33.5) | 87.7 (32.7) | 62.9 (43.1) | 65.5 (39.7) |
| 24 | 63.9 (43.7) | 58.3 (47.1) | 43.3 (39.3) | 45.5 (55.4) |
| 30 | 40.0 (38.5) | 41.0 (43.9) | 28.8 (33.1) | 31.7 (42.6) |
| 36 | 24.3 (52.5) | 29.0 (53.6) | 18.1 (56.8) | 22.4 (69.5) |
| 48 | 13.9 (99.9) | 17.3 (75.5) | 10.8 (77.9) | 12.4 (114.4) |

| | | | | | 90% CI |
|---|---|---|---|---|---|
| AUC(0-48) (ng.hr/mL) | 3744(27) | 3908(22) | 3636(23) | 3883(27) | |
| AUCinf (ng.hr/mL) | 3869(28) | 4052(22) | 3699(23) | 3976(28) | |
| Cmax(ng/mL) | 340.9(33) | 352.0(24) | 391.3(35) | 433.8(36) | |
| Tmax (hr) | 3.0 | 3.5 | 3.8 | 4.0 | |
| LnAUC(0-48)(Fasting) | | | | | 94.3-115.5 |
| LnAUCinf (Fasting) | | | | | 94.5-116.4 |
| LnCmax (Fasting) | | | | | 92.1-115.7 |
| C/A (Nonfasting) | | | | | |
| AUC(0-48) | | | | | 1.07 |
| AUCinf | | | | | 1.07 |
| Cmax | | | | | 1.01 |

Morphine-6-Glucuronide (M-6-G)

1. For M-6-G, the least squares means for AUC(0-48), AUCinf and Cmax values were 3.4%, 5.1% and 1.6% higher, respectively, for the test product than for the reference product under fasting conditions. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The M-6-G plasma levels peaked at 3 hours for both the test and reference products under fasting conditions.

3. For AB Generics' test product, the least squares means for AUC(0-48), AUCinf and Cmax values were 5.9%, 6.5% and 9.4% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-48), AUCinf and Cmax.

4. The M-6-G plasma levels peaked at 3.5 and 4 hours for the the reference and test products, respectively, under nonfasting conditions.

5. For the test and reference products, the mean Cmax values after dosing with food were about 123.2% and 114.8%, respectively, of the values reported in the fasting state. Also, after feeding the Tmax were delayed about 0.5 and 0.8 hours, for the test and reference product, respectively, relative to the Tmax reported under fasting conditions.

V. Study #MO94-0309, Multiple-dose Bioequivalence study of Morphine Sulfate Controlled-Release 200 mg Tablets

The objective of the study was to assess the bioavailablity at steady-state of Morphine Sulfate Controlled-release 200 mg tablets (AB Generics) as compared to MS Contin$^{R}$ (controlled-release morphine sulfate) 200 mg Tablets (Purdue Frederick Company) following twice-a-day dosing of each formulation for four days.

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| Clinical site: | (b)(4)(CC) |
| Analytical site: | |
| Dose dates: | May 31, 1994 and June 9, 1994 |
| Analysis dates: | June 8-July 21, 1994 |
| Investigator: | Same as Study #MO93-0602 above |
| Study design: | Two-way crossover, multiple-dose study |

| | |
|---|---|
| Subjects: | Twenty-two healthy male and female subjects were enrolled after compliance with the inclusion and exclusion criteria for study participation. Eleven (11) males and 11 females were selected. Five (5) subjects were Hispanic and seventeen (17) were Caucasian. Twenty-one successfully completed the study. Subject #3 tested positive for benzodiazepines prior to period II dosing and did not complete the study. |
| Selection criteria, Exclusion criteria, and Restrictions: | Please see study #MO93-0602 for the single dose. |
| Washout period: | One week |
| Dose and treatment: | Test Product.<br>Days 1-3: 1x200 mg Morphine Sulfate Controlled-Release Tablet (Purdue Frederick Company), lot #4WD, Exp.10/95 administered twice-a-day with 240 mL of water at 8 AM and 8 PM.<br>Day 4: 1x200 mg Morphine Sulfate Controlled-Release Tablet (Purdue Frederick Company), lot #4WD, Exp.10/95 administered with 240 mL of water.<br>Reference Product.<br>Days 1-3: 1x200 mg MS Contin$^{R}$ (morphine sulfate controlled-release) Tablet (Purdue Frederick Company), lot #3GP, Exp.12/94 administered twice-a-day with 240 mL of water at 8 AM and 8 PM.<br>Day 4: 1x200 mg MS Contin$^{R}$ (Purdue Frederick Company), lot #3GP, Exp.12/94 administered with 240 mL of water. |
| Other Medications: | The subjects underwent a urine screen prior to Period I and, if negative, were then administered a Narcan$^{R}$ challenge test. The latter was done prior to receiving test medication and before receiving the first dose of Trexan$^{TM}$. Trexan$^{TM}$ and test medication were not to be administered to any subject showing clinical signs of opioid withdrawal or a positive urine drug test for opiods. The Narcan$^{R}$ challenge test was administered intravenously with an initial 0.2 mg. The subject was observed for evidence of sign or symptoms of withdrawal for 30 seconds. If no evidence of withdrawal was apparent then the |

remaining 0.6 mg of Narcan® was injected and observation for signs or symptoms of withdrawal continued for 20 minutes. Once it was determined that a subject was opioid-free, and not physically dependent, naltrexone (Trexan™; 2x50 mg tablets) was administered 24 hours prior to the first study drug administration, then at the time of each subsequent dosing (1x50 mg tablet) and again 12 and 24 hours after the last dose of study medication on day 4 (1x50 mg tablet). The Trexan™ administration occurred during each of the two periods of the study.

Food intake:

The subjects entered the testing facility at least 26 hours prior to initial dosing with test medication for period I of the study and were confined there until the morning on Day 5. On Days 1-4, the subjects observed a 10-hour fast preceding and a 4-hour fast following morning administration of the assigned drug; on Days 1-3 they observed a 2-hour fast preceding and following evening dosing. They were then allowed a standardized meal at pre-determined times. Drug administration occurred at 0800 hours on Days 1-4 and at 2000 hours on day 1, 2 and 3.

Blood samples:

Ten (10) mL of blood were collected during each study period at:
Day 1: 0 hour (pre-drug)
Day 2: 0 hour (pre-drug)
Day 3: 0 hour (pre-drug)
Day 4: 0 hour (pre-drug), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 hours post-dose on Day 4. Plasma samples were separated and stored at -20°C.

Assay Methodology:

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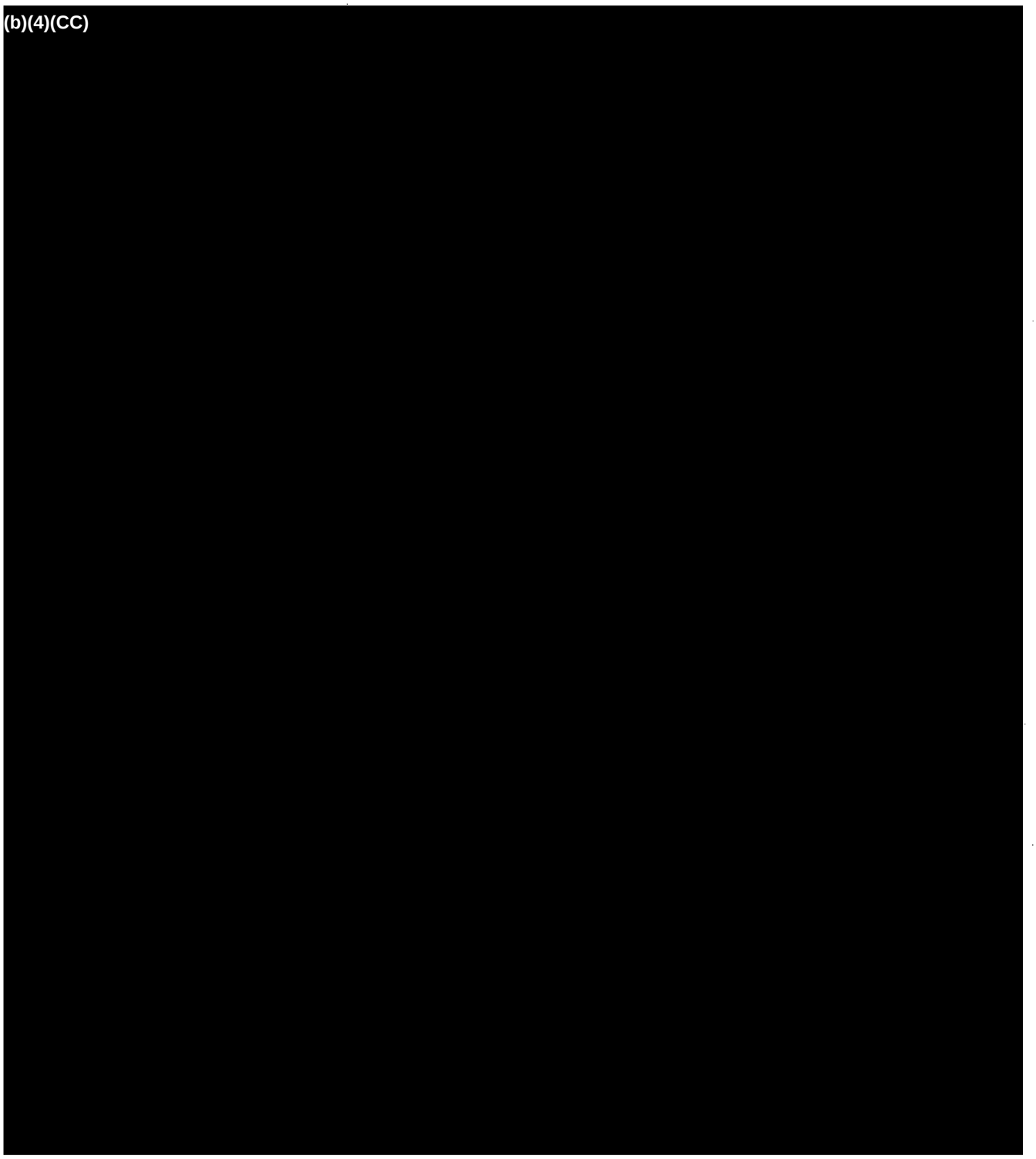


Statistical Analysis:

Statistical analysis was performed using SAS-GLM. ANOVA was performed using GLM. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two one-sided

tests were used to estimate the 90% confidence interval for the pharmacokinetic parameters. The attainment of steady-state was evaluated by subject for each treatment period using the plasma concentration values obtained just prior (within 15 minutes) to the 8 am dose on Days 2, 3, and 4. A least squares line was fitted and the slope estimated. Any subjects with a significant positive slope were flagged for non-attainment of steady-state.

Vital Signs: The oral temperature, respiratory rate, sitting pulse, and systolic and diastolic blood pressures were measured within 30 minutes prior to dosing on each day and then again at the following times after the Day 4 dose: 12, 24, 36, 48, 60, 72, 74, 80, 84 and 96 hours.

VI. In Vivo Results

Twenty-two (22) subjects were enrolled in this study and twenty-one successfully completed it. Subject #3 tested positive for benzodiazepines prior to period II dosing and did not complete the study. There were 10 male and 11 female subjects completing the study. Subjects 2, 9, 11, 14, 15, 18 and 19 all tested positive for opiates prior to period 2; this was considered due to the relatively high dose (400 mg daily) of morphine taken during the preceding study period. These subjects were allowed to continue in the study. Forty-nine (49) adverse experiences were reported by 21 subjects during the two periods. Eight of the events were rated as moderate in severity and 41 as mild, in the opinion of the investigator. Six of the events were judged as unrelated to use of study drug, 14 as possibly related and 29 as probably related. None was considered definitely related. There were no reports of severe, serious or unexpected side effects. There were no apparent differences in incidence or nature of adverse experiences between the test and reference products. The most frequent adverse experiences were headache (6 subjects; 9 reports), nausea (8 subjects; 9 reports), lightheadedness (5 subjects; 6 reports), drowsiness (6 subjects; 6 reports), vasovagal episode (3 subjects; 4 reports), paresthesia, flushed sensation and tiredness (2 subjects; 2 reports each).
The results also indicate that the incidence of adverse experiences were similar between the test and reference drugs under steady-state dosing conditions for both male and female subjects. Except for an increased incidence of nausea among females (7 reports by 7 subjects vs. 2 reports by 1 subject among males) and vasovagal episodes (3 reports by 2 female subjects vs. 1 report by 1 subject among males), there were no striking differences between the gender groups in the incidence and nature of the reports.

The plasma concentrations and pharmacokinetic parameters for Morphine and Morphine-6-Glucuronide are summarized in Tables III and IV.

Table III

Mean Morphine Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (7x200 mg Tablet) of Morphine Sulfate Controlled Release Tablets
(N=21)

| Time | Reference MS Contin® Lot #3GP ng/mL (CV) | Test Morphine Sulfate Lot #4WD ng/mL (CV) |
|---|---|---|
| Day 1-0 hr | 0.00 | 0.00 |
| Day 2-0 hr | 52.23 (43.6) | 56.97 (56.6) |
| Day 3-0 hr | 63.75 (39.3) | 69.51 (52.0) |
| Day 4-0 hr | 81.94 (35.5) | 74.81 (39.5) |
| 0.5 hr | 122.56 (35.0) | 117.33 (47.3) |
| 1 hr | 151.80 (34.3) | 133.43 (37.7) |
| 1.5 hr | 148.44 (33.9) | 144.41 (31.7) |
| 2 hr | 136.77 (28.1) | 152.46 (33.3) |
| 2.5 hr | 141.58 (25.9) | 148.59 (41.4) |
| 3 hr | 140.90 (31.3) | 142.65 (38.9) |
| 3.5 hr | 139.05 (33.3) | 136.03 (36.5) |
| 4 hr | 131.97 (33.9) | 142.54 (42.3) |
| 5 hr | 135.18 (39.7) | 140.83 (39.0) |
| 6 hr | 102.20 (32.8) | 117.69 (34.7) |
| 8 hr | 85.42 (37.8) | 92.08 (50.7) |
| 10 hr | 72.86 (31.4) | 78.22 (43.8) |
| 12 hr | 68.46 (37.2) | 61.91 (31.6) |

| | | | 90% CI |
|---|---|---|---|
| AUC(0-12)(ng.hr/mL) | 1283.5 (28.0) | 1332.8 (30.9) | |
| Cmax (ng/mL) | 186.3 (24.3) | 190.2 (29.3) | |
| Cmin (ng/mL) | 75.2 (32.8) | 68.4 (29.6) | |
| Tmax (hr) | 2.19(57.5) | 2.76(70.1) | |
| Fluct* (%) | 155.5 (28.8) | 181.4 (20.5) | |
| LnAUC(0-12) | | | 95.6-111.3% |
| LnCmax | | | 91.7-111.5% |

*Fluct = (Cmax-Cmin)/Cmin X 100
Cmin = Mean of the zero and 12 hour values of the plasma analyte concentration measured on day 4.

Morphine

1. The plasma morphine levels peaked at 1 and 2 hours for the reference and the test products, respectively.

2. An analysis of steady-state attainment was performed using the

plasma concentration values obtained just prior (within 15 minutes) to the 8 am dose on Days 2, 3, and 4. Subject #19 had trough plasma morphine levels which showed a significant increase slope. The subject's trough values were included in the calculation of a mean slope for the study group, yet the overall mean did not show a significant increasing slope for plasma levels on this treatment. Subject #19 was included in the statistical analysis of the study.

3. For Morphine, the least squares means for AUC(0-12) and Cmax values were 4.1% and 2.3% higher, respectively, for the test product than for the reference product. The differences were not statistically significant, the 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

Table IV

Mean M-6-G Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (7x200 mg Tablet) of Morphine Sulfate Controlled Release Tablets
(N=21)

| Time | Reference MS Contin® Lot #3GP ng/mL (CV) | Test Morphine Sulfate Lot #4WD ng/mL (CV) |
|---|---|---|
| Day 1-0 hr | 0.00 | 0.00 |
| Day 2-0 hr | 194.76 (57.6) | 202.61 (49.1) |
| Day 3-0 hr | 236.81 (51.6) | 241.06 (42.6) |
| Day 4-0 hr | 270.30 (45.2) | 271.97 (39.1) |
| 0.5 hr | 283.09 (41.9) | 265.61 (38.8) |
| 1 hr | 394.02 (34.8) | 371.89 (30.6) |
| 1.5 hr | 470.31 (31.7) | 484.98 (28.3) |
| 2 hr | 538.59 (26.1) | 544.27 (33.8) |
| 2.5 hr | 560.91 (27.7) | 542.99 (31.2) |
| 3 hr | 565.57 (26.8) | 565.38 (33.3) |
| 3.5 hr | 560.94 (29.7) | 551.54 (28.5) |
| 4 hr | 554.43 (29.9) | 567.78 (30.2) |
| 5 hr | 506.19 (28.2) | 503.76 (33.5) |
| 6 hr | 414.45 (29.6) | 433.92 (33.3) |
| 8 hr | 335.89 (49.4) | 325.82 (37.0) |
| 10 hr | 314.13 (48.8) | 274.34 (36.6) |
| 12 hr | 252.62 (38.5) | 239.84 (42.1) |
| AUC(0-12)(ng.hr/mL) | 4850.6 (29.1) | 4755.1 (25.7) |
| Cmax (ng/mL) | 664.6 (23.6) | 682.7 (26.7) |
| Cmin (ng/mL) | 261.5 (31.8) | 255.9 (35.7) |
| Tmax (hr) | 3.14(31.9) | 3.05(34.0) |

| | | | |
|---|---|---|---|
| Fluct* (%) | 166.7 (38.1) | 181.8 (35.7) | |
| LnAUC(0-12) | | | 87.1-112.7% |
| LnCmax | | | 89.9-116.4% |

*Fluct = (Cmax-Cmin)/Cmin X 100
Cmin = Mean of the zero and 12 hour values of the plasma analyte concentration measured on day 4.

Morphine-6-Glucuronide (M-6-G)

1. The plasma M-6-G levels peaked at 3 hours for both the test and the reference products.

2. The least squares means for AUC(0-12) and Cmax values were 1.4% and 3.1% lower and higher, respectively, for the test product than for the reference product. The differences were not statistically significant. The 90% confidence intervals for AUC(0-12) and Cmax are within the acceptable range of 80-125%.

VII. Formulations: **Not To Be Release Under FOI**

The formulations of AB Generics L.P. and Purdue Frederick for Morphine Sulfate Controlled-Release Tables, 200 mg are shown below:

| Component | AB Generics L.P. Morphine Sulfate Controlled-Release Tablets 200 mg | Purdue Frederick MS Contin® Morphine Sulfate Controlled-Release Tablets 200 mg |
|---|---|---|
| Morphine Sulfate (Pentahydrate), USP | 200.0 mg | 200.0 mg |
| Hydroxyethyl Cellulose, NF<br>Cetostearyl Alcohol, NF<br>Talc, USP<br>Magnesium Stearate, NF<br>Purified Water, USP | (b)(4)(TS) | |
| Colorant | | |
| Purified Water, USP | * | * |
| (b)(4)(TS) | Lt. Green**<br>Green** | (b)(4)(TS) |

* Appears in the finished dosage form as residual moisture.
** Side-by-side qualitative comparison of colorant compositions are shown below:

(b)(4)(TS)

VIII. In vitro Dissolution Testing:

| | |
|---|---|
| Method: | USP 23 apparatus I (basket) at 50 rpm |
| Medium: | 900 mL of Simulated Gastric Fluid for 1, 2, 3, 4, 6, 8, 9 and 12 hours. |
| Number of Tablets: | 12 |
| Test Product: | AB Generics' Morphine Sulfate Controlled-Release tablets, 200 mg, Lot #4WD. |
| Reference Product: | Purdue's MS Contin® Morphine Sulfate Controlled-Release tablets, 200 mg, Lot #3GP |

The dissolution testing results are presented in table V.

IX. Comments:

1. The firm's single-dose, four-way crossover bioequivalence study #MO93-0602 under fasting and nonfasting conditions, conducted on its 200 mg morphine sulfate controlled-release, 200 mg tablet is a substitute of two bioequivalence studies, i.e., a single dose bioequivalence study under fasting conditions and a single dose post-prandial bioequivalence study.

2. In the single-dose bioequivalence study #MO93-0602, the firm calculated $AUC_{0-48}$ and not $AUC_{0-t}$ by the trapezoidal rule. The AUC(0-inf) was estimated as follows:

a. If C(48)$\leq$ 0, the AUC(0-48) was taken as AUC(0-inf).
B. If C(48)> 0, then the quantity C(48)/kel was added to AUC(0-48) to estimate AUC(0-inf), where Kel is the terminal first order apparent elimination rate constant.

By using the above calculation method the values of $AUC_{0-48}$ are the same as AUC(0-inf) values for some subjects.

3. The in vitro dissolution testing for the test product 200 mg Morphine Sulfate Controlled-Release 200 tablets is acceptable.

X. Deficiency Comment:

The following comments apply to the two biostudies evaluated above:

1. The firm has indicated that the morphine sulfate controlled-release 200 mg tablet, lot #4WD, Purdue Frederick Company, is the test product used in the bioequivalence studies. The firm is advised to clarify that the test product is AB Generics' product and not Purdue Frederick's product.

2 The potency and content uniformity for the test and reference products should be submitted.

3. The firm is advised to submit the analytical raw data for all subjects in the studies.

4. The firm is advised to submit its criteria for acceptance of batch runs based on standard curves and quality controls samples used for morphine and morphine-6-glucuronide (study #MO94-0309) and for morphine-6-glucuronide (study #MO93-0602).

5. The firm is advised to submit 3.5" Diskettes in ASCII code for the bioequivalence studies # MO93-0602 and #MO94-0309.

The following comments apply to the single-dose, study# MO93-0602:

1. The following pharmacokinetic parameters should be submitted for morphine and morphine-6-glucuronide, T1/2, Kel, $AUC_{0-t}$ (area under the plasma concentration-time curve from time zero to time t, calculated by the trapezoidal rule, where t is the last measurable time point) and $AUC_{0-inf}$ (where $AUC_{0-inf} = AUC_t + C_t/Kel$, $C_t$ is the last measurable drug concentration and Kel is the terminal elimination rate constant calculated according to an appropriate method).

2. For morphine-6-glucuronide, the standard curve and controls were aliquoted in 0.5 mL volumes. The unknown samples volumes were aliquoted as following:

| Period, Subjects | Time(hr) | Volume(mL) |
|---|---|---|
| (b)(4)(CC) | | |

(b)(4)(CC)

[redacted] t validates the above

3. The representative (b)(4)(CC) [redacted] of morphine for subject #14 (study #MO93-0602) are incomplete. The firm should submit the following missing (b)(4)(CC) [redacted] for the following time points and controls:

(b)(4)(CC)

[redacted]

4. In the representative (b)(4)(CC) [redacted] of morphine for subject #2 (study #MO93-0602), the amount of morphine reported for the quality control sample "#29 67 morph2.m 1 ctr 63" was 128.9 ng/mL. The 128.9 ng/mL morphine value is probably a value of a high (125 ng/mL) quality control sample and not for quality control sample of 63 ng/mL morphine. The firm should clarify this discrepancy.

The following comments apply to the steady-state, study# MO94-0309:

1. The original plasma sample volumes used for morphine extraction of the unknown samples were 0.25 mL and 0.1 mL. In both cases, (0.25 mL and 0.1 mL) blank plasma was used to bring the total sample volume to 1.0 mL as is described in the analytical method. The firm is advised to submit data that validate the above dilutions.

2. For morphine-6-glucuronide, standard curve and control samples were aliquoted in 0.5 mL volumes while the unknown sample volumes were aliquoted at 0.05 mL to avoid surpassing the calibration range. The firm is advised to submit data that validate the above dilution.

XI. Recommendations:

1. The single-dose bioequivalence study #MO93-0602, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 200 mg tablets, lot #4WD, comparing it to MS Contin® Controlled-Release 200 mg tablets manufactured by Purdue Frederick Company,

has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comments.

2. The multiple-dose steady-state bioequivalence study #MO94-0309, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 200 mg tablets, lot #4WD, comparing it to MS Contin$^{R}$ Controlled-Release 200 mg tablets manufactured by Purdue Frederick Company, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comments.

3. The dissolution testing conducted by AB Generics L.P., on its Morphine Sulfate Controlled-Release 200 mg tablets, lot #4WD, is acceptable. The dissolution testing should be conducted in 900 mL of simulated gastric fluid at 37$^{0}$C using USP 23 apparatus I (basket) at 50 rpm. Based on the submitted data the following tentative specifications are recommended:

| | | |
|---|---|---|
| 1 | hour | (b)(4)(CC) [redacted] |
| 2 | hours | |
| 3 | hours | |
| 4 | hours | |
| 8 | hours | |

4. From the bioequivalence point of view the firm has not met the requirements of in vivo testing for the reasons given in deficiency comments and the bioequivalence data are incomplete.

The firm should be informed of the deficiency comments and recommendations.

/S/ [redacted]
Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ [redacted] Date: 3/26/96

Concur: /S/ [redacted] 4/17/96 Date:
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/3-25-96 wp 74769SD.095
cc: ANDA #74-769, original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

**Table V In Vitro Dissolution Testing**

Drug (Generic Name): Morphine sulfate Controlled-Release Tablets, 200 mg
Dose Strength:200 mg Tablets
ANDA No.:74-769
Firm: A.B. Generics L.P.
Submission Date: October 16, 1995
File Name: 74769SD.095

I. Conditions for Dissolution Testing:

USP 23 Basket: X Paddle: RPM: 50
No. Units Tested: 12
Medium:900 mL SGF for 1, 2, 3, 4, 6, 8, 9 and 12 hours
Specifications:
Reference Drug: Purdue Frederick's MS Contin
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

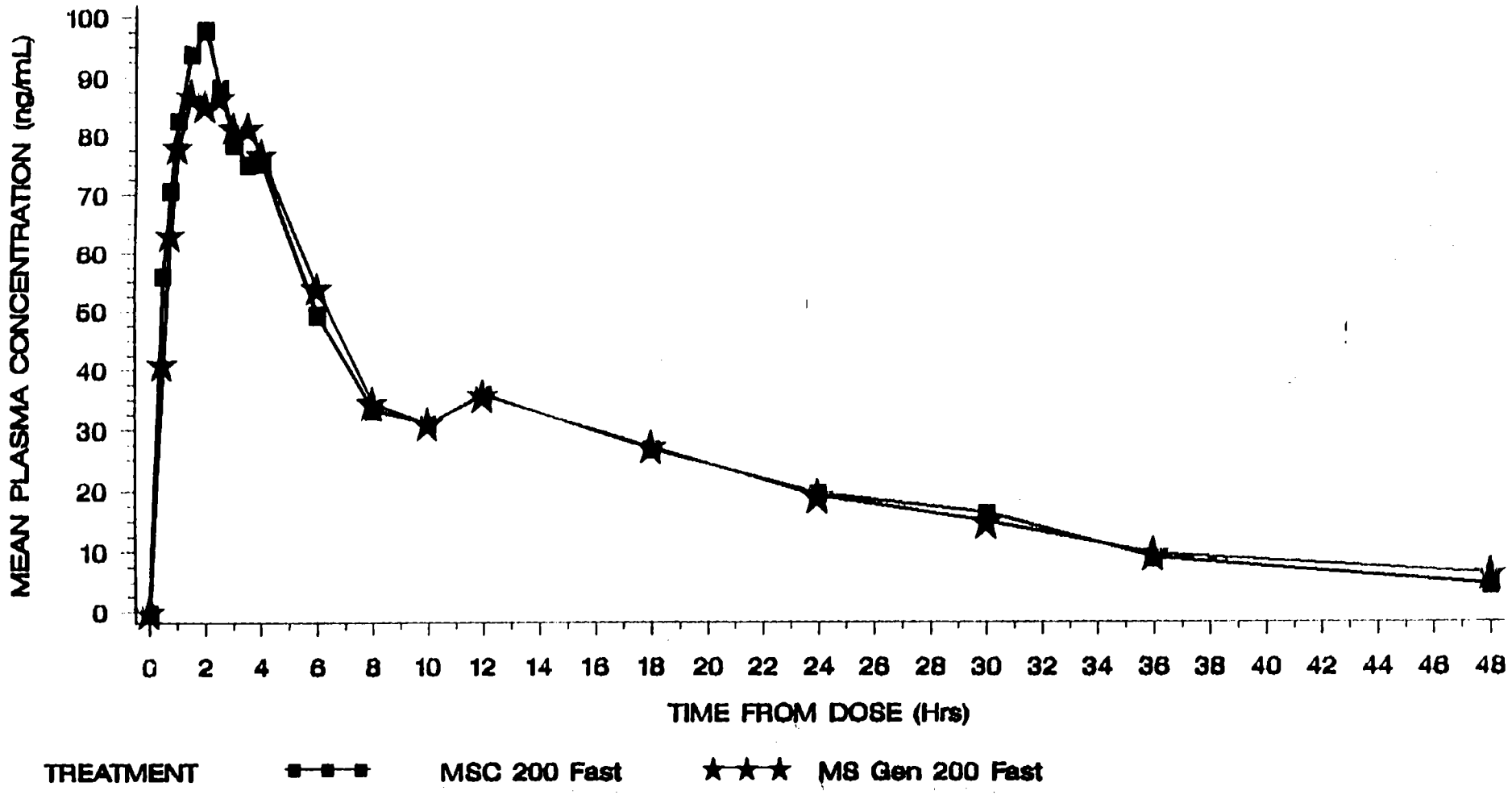
| Sampling Times (hr) | Test Product Lot #4WD Strength(mg) 200 | | | Reference Product Lot # 3GP Strength(mg) 200 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 1 | 28.8 | (b)(4)(CC) | 1.0 | 27.8 | (b)(4)(CC) | 5.1 |
| 2 | 45.3 | | 1.7 | 43.1 | | 3.7 |
| 3 | 57.4 | | 1.0 | 54.8 | | 2.9 |
| 4 | 66.8 | | 0.9 | 64.3 | | 2.5 |
| 6 | 82.0 | | 1.3 | 79.3 | | 1.8 |
| 8 | 92.8 | | 1.8 | 89.8 | | 1.2 |
| 9 | 96.7 | | 1.9 | 93.8 | | 1.1 |
| 12 | 103.6 | | 2.4 | 101.3 | | 0.78 |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

PROTOCOL NO. MO93-0602

FIGURE I

MEAN PLASMA MORPHINE CONCENTRATION (NG/ML) OVER TIME – FASTED

Population: Valid for Pharmacokinetic & Safety Analysis



PROTOCOL NO. MO93-0602

FIGURE II

MEAN PLASMA MORPHINE CONCENTRATION (NG/ML) OVER TIME - FED

Population: Valid for Pharmacokinetic & Safety Analysis

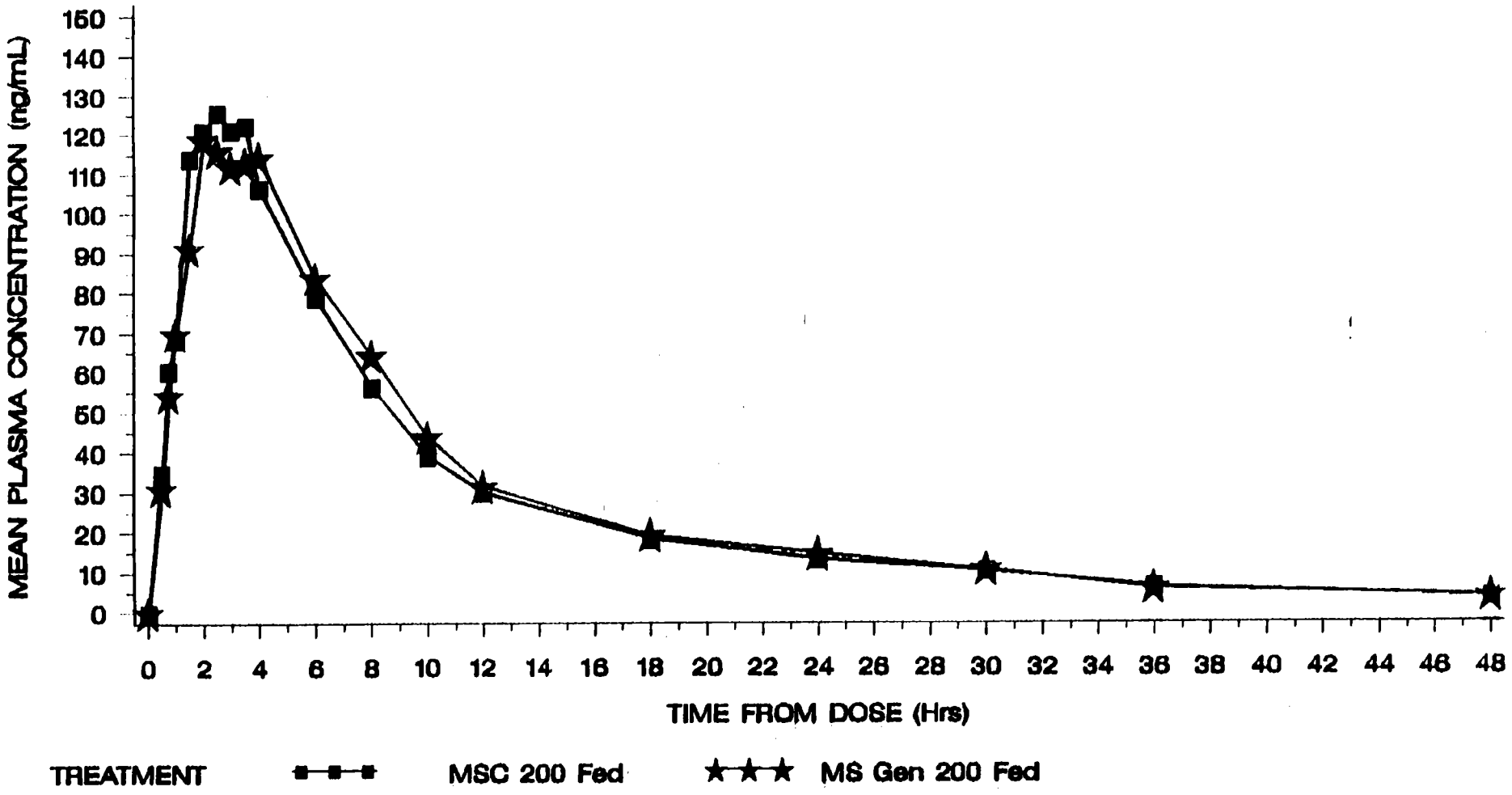
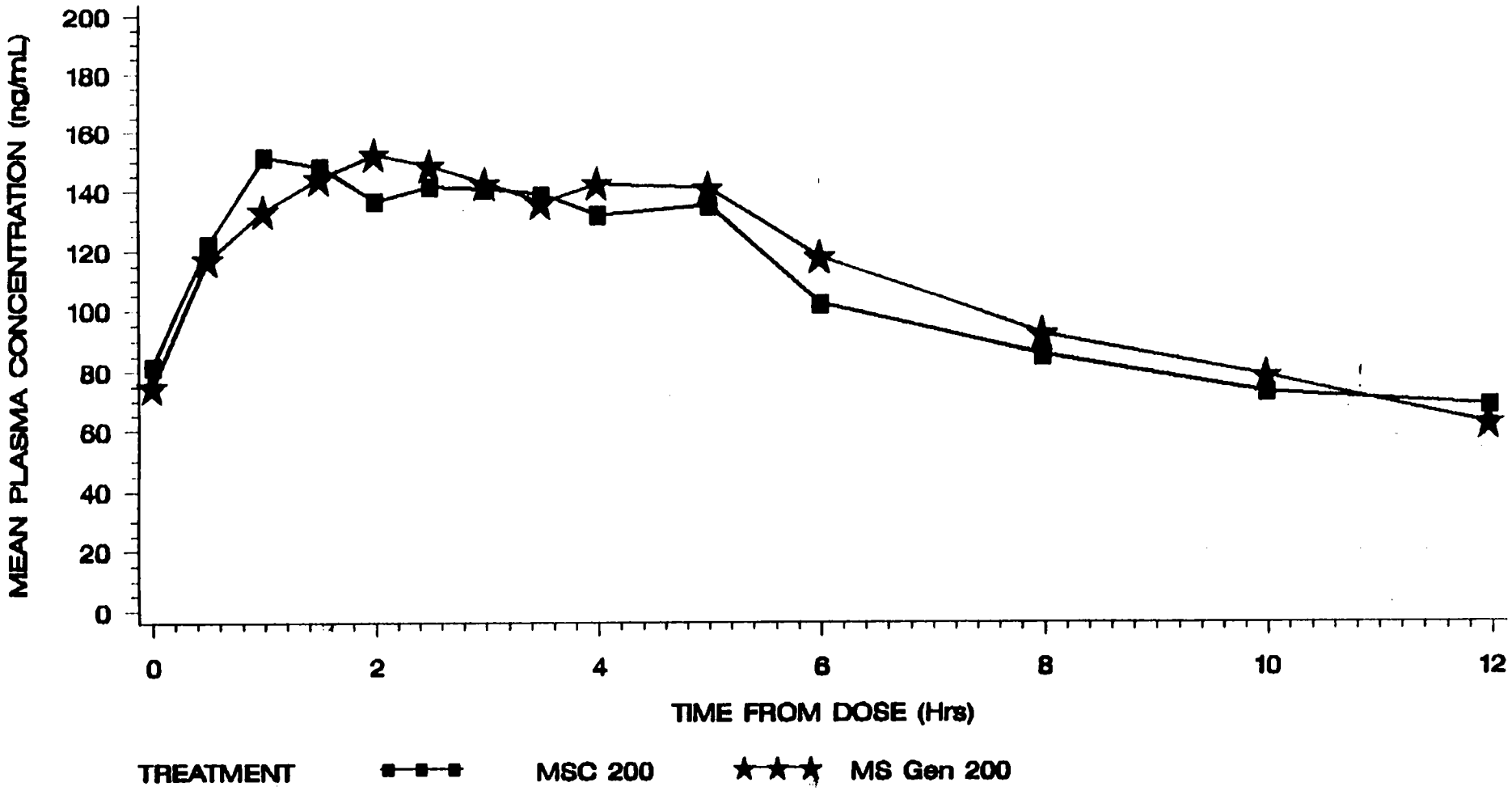


FIGURE I

MEAN PLASMA MORPHINE CONCENTRATION (NG/ML) OVER TIME

Population: Valid for Pharmacokinetic & Safety Analysis

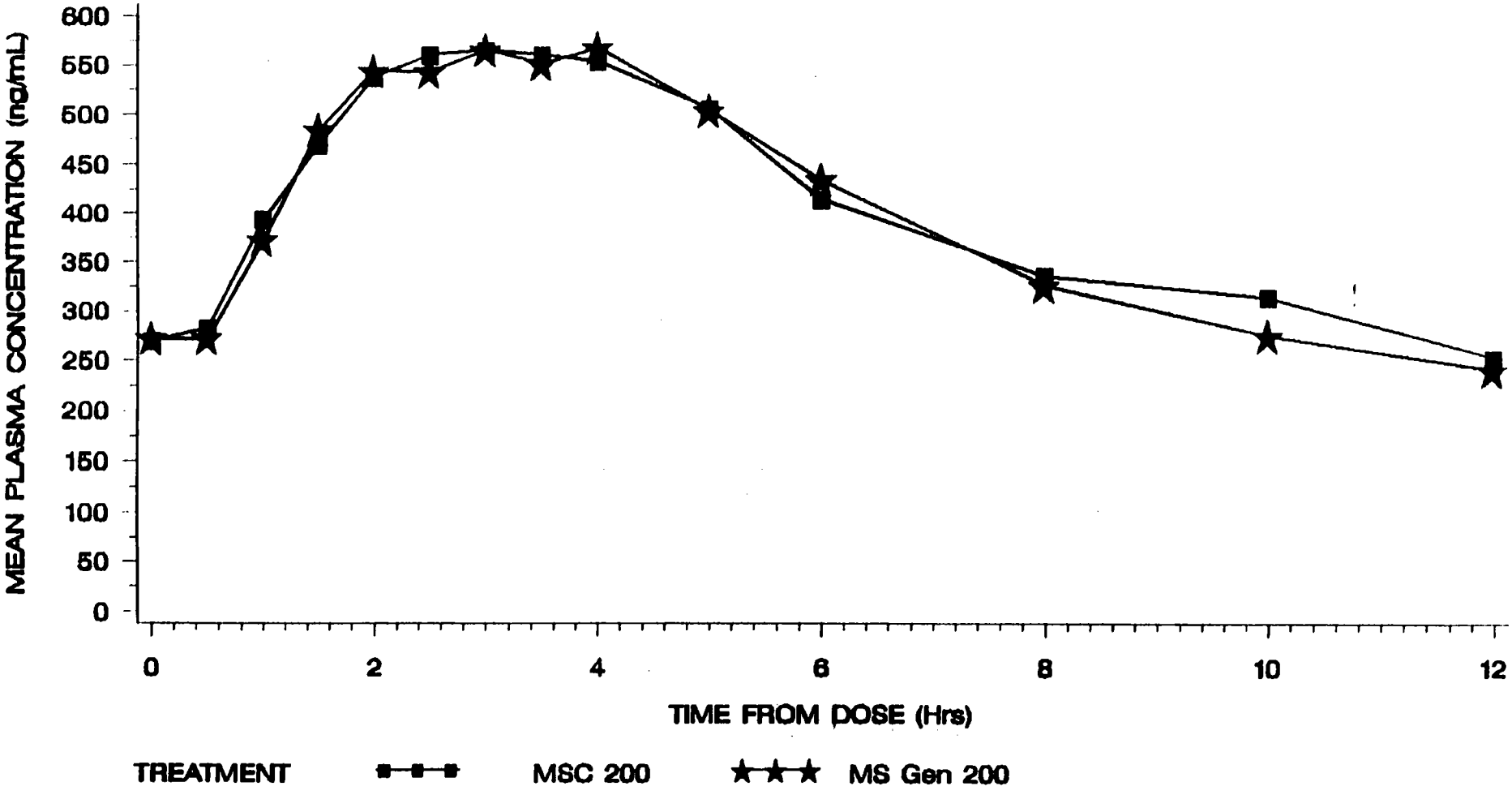


PROTOCOL NO. MO94-0309

FIGURE II

MEAN PLASMA MORPHINE-6-GLUCURONIDE CONCENTRATION (NG/ML) OVER TIME

Population: Valid for Pharmacokinetic & Safety Analysis



PROTOCOL NO. MO94-0309

TABLE 7

ADVERSE EXPERIENCES BY SUBJECT

Population: All Subjects Valid for Safety Analysis

INVESTIGATOR NUMBER: 660
PHASE: Visit 1

| SUBJECT NUMBER | SEX | ADVERSE EXPERIENCE | SEVERITY | ONSET DATE | ONSET TIME | STOP DATE | DURATION HOUR | DURATION MIN | RELATIONSHIP TO TEST MED | TEST MED. ACTION TAKEN | STATUS | OTHER ACTION TAKEN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TREATMENT GROUP: MSC 200mg | | | | | | | | | | | | |
| 1 | M | HEADACHE | Mild | 05/31/94 | 20:50 | 05/31/94 | 1 | 12 | Poss. | None | Recovered | None |
| | M | HEADACHE | Mild | 06/02/94 | 10:16 | 06/02/94 | 6 | 39 | Poss. | None | Recovered | None |
| | M | NAUSEA | Mild | 06/02/94 | 10:16 | 06/02/94 | 2 | 14 | Prob. | None | Recovered | None |
| | M | NAUSEA | Moderate | 06/02/94 | 12:30 | 06/02/94 | 4 | | Prob. | None | Recovered | None |
| 8 | F | DRY EYES | Mild | 06/02/94 | 10:35 | 06/02/94 | 2 | 10 | Poss. | None | Recovered | None |
| 20 | M | LIGHTHEADEDNESS | Mild | 06/02/94 | 13:27 | 06/02/94 | | 33 | Prob. | None | Recovered | Other |
| 22 | F | DROWSINESS | Mild | 05/31/94 | 18:00 | 06/02/94 | | | Prob. | None | Recovered | None |
| TREATMENT GROUP: MS Gen 200mg | | | | | | | | | | | | |
| 2 | F | NAUSEA | Mild | 06/02/94 | 11:04 | 06/02/94 | 2 | 11 | Prob. | None | Recovered | None |
| 4 | F | EYE IRRITATION | Mild | 06/02/94 | 10:00 | 06/02/94 | | 34 | None | None | Recovered | None |
| 5 | F | DROWSINESS | Mild | 05/30/94 | 10:00 | 06/02/94 | | | Prob. | None | Recovered | None |
| | F | NAUSEA | Mild | 06/02/94 | 12:16 | 06/02/94 | | 56 | Prob. | None | Recovered | None |
| 12 | M | DROWSINESS | Mild | 06/02/94 | 10:00 | 06/02/94 | 9 | | Prob. | None | Recovered | None |
| | M | LIGHTHEADEDNESS | Mild | 06/02/94 | 11:20 | 06/02/94 | 1 | 18 | Prob. | None | Recovered | Other |
| 13 | F | PARESTHESIA | Mild | 05/30/94 | 23:00 | 05/30/94 | | 24 | Prob. | None | Recovered | None |
| | F | LIGHTHEADEDNESS | Moderate | 05/30/94 | 23:05 | 05/30/94 | | 20 | Prob. | None | Recovered | Other |
| | F | LIGHTHEADEDNESS | Mild | 05/30/94 | 23:25 | 05/30/94 | | 20 | Prob. | None | Recovered | None |
| | F | TIREDNESS | Mild | 05/31/94 | 10:58 | 05/31/94 | 6 | 32 | Prob. | None | Recovered | None |
| | F | HEADACHE | Mild | 05/31/94 | 11:26 | 05/31/94 | 6 | 4 | Poss. | None | Recovered | None |
| | F | ABDOMINAL BLOATING | Mild | 06/01/94 | 18:56 | 06/01/94 | 2 | 4 | Poss. | None | Recovered | None |
| | F | HEADACHE | Mild | 06/02/94 | 10:50 | 06/02/94 | 1 | 16 | Poss. | None | Recovered | None |
| | F | VASOVAGAL EPISODE | Mild | 06/02/94 | 11:42 | 06/02/94 | | 24 | None | None | Recovered | Other |
| 14 | F | NAUSEA | Moderate | 05/30/94 | 13:50 | 05/31/94 | 22 | 10 | Prob. | None | Recovered | Other |
| | F | VOMITING | Moderate | 05/30/94 | 14:45 | 05/31/94 | 10 | 5 | Prob. | None | Recovered | Other |
| | F | SPOTTING | Mild | 05/31/94 | 9:25 | 06/01/94 | 23 | 56 | None | None | Recovered | Other |
| | F | EUPHORIA | Mild | 05/31/94 | 12:00 | 06/01/94 | 12 | | Prob. | None | Recovered | None |
| 19 | F | LIGHTHEADEDNESS | Mild | 05/30/94 | 19:00 | 06/02/94 | | | Prob. | None | Recovered | Other |



(Continued)

PROTOCOL NO. M094-0309

TABLE 7

ADVERSE EXPERIENCES BY SUBJECT

Population: All Subjects Valid for Safety Analysis

INVESTIGATOR NUMBER: 660
PHASE: Visit 1

| SUBJECT NUMBER | SEX | ADVERSE EXPERIENCE | SEVERITY | ONSET DATE | ONSET TIME | STOP DATE | DURATION HOUR | DURATION MIN | RELATIONSHIP TO TEST MED | TEST MED. ACTION TAKEN | STATUS | OTHER ACTION TAKEN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TREATMENT GROUP: MS Gen 200mg | | | | | | | | | | | | |
| (19) | F | ABDOMINAL PAIN | Mild | 05/30/94 | 21:00 | 05/31/94 | 10 | | Poss. | None | Recovered | None |
| | F | PARESTHESIA | Mild | 06/03/94 | 14:00 | 06/04/94 | | | Prob. | None | Recovered | None |
| 21 * | F | DROWSINESS | Mild | 05/30/94 | | 06/02/94 | | | Prob. | None | Recovered | None |
| | F | HEADACHE | Mild | 06/01/94 | 9:00 | 06/01/94 | 5 | 5 | Poss. | None | Recovered | None |
| TREATMENT GROUP: Naltrexone HCl | | | | | | | | | | | | |
| 2 | F | DIARRHEA | Mild | 05/29/94 | 8:00 | 06/06/94 | | | None | None | Recovered | None |
| | F | DYSPEPSIA | Mild | 05/29/94 | 8:00 | 06/06/94 | | | None | None | Recovered | None |



(continued)

PROTOCOL NO. M094-0309

TABLE 7

ADVERSE EXPERIENCES BY SUBJECT

Population: All Subjects Valid for Safety Analysis

INVESTIGATOR NUMBER: 660
PHASE: Visit 2

| SUBJECT NUMBER | SEX | ADVERSE EXPERIENCE | SEVERITY | ONSET DATE | ONSET TIME | STOP DATE | DURATION HOUR | DURATION MIN | RELATIONSHIP TO TEST MED | TEST MED. ACTION TAKEN | STATUS | OTHER ACTION TAKEN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TREATMENT GROUP: MSC 200mg | | | | | | | | | | | | |
| (2) | F | HEADACHE | Moderate | 06/09/94 | 13:00 | 06/09/94 | 8 | 3 | Poss. | None | Recovered | None |
| | F | NAUSEA | Mild | 06/09/94 | 14:20 | 06/09/94 | 3 | 25 | Prob. | None | Recovered | None |
| | F | HEADACHE | Mild | 06/10/94 | 13:00 | 06/10/94 | 6 | 38 | Poss. | None | Recovered | None |
| | F | FLUSHED SENSATION | Mild | 06/10/94 | 15:15 | 06/10/94 | | 45 | Prob. | None | Recovered | Other |
| | F | MYALGIA | Mild | 06/13/94 | 6:30 | 06/14/94 | | | Poss. | None | Recovered | None |
| 5 | F | NAUSEA | Mild | 06/12/94 | 11:12 | 06/12/94 | 3 | 12 | Prob. | None | Recovered | None |
| (9) | M | VASOVAGAL EPISODE | Moderate | 06/10/94 | 9:23 | 06/10/94 | | 18 | None | None | Recovered | Other |
| (14) | F | HEADACHE | Mild | 06/09/94 | 18:15 | 06/11/94 | | | Poss. | None | Recovered | Other |
| | F | NAUSEA | Moderate | 06/10/94 | 15:50 | 06/10/94 | | 20 | Prob. | None | Recovered | Other |
| | F | VOMITING | Moderate | 06/10/94 | 16:05 | 06/10/94 | | 3 | Prob. | None | Recovered | None |
| 18 | M | FLUSHED SENSATION | Mild | 06/10/94 | 15:00 | 06/11/94 | 10 | | Prob. | None | Recovered | None |
| | M | JITTERINESS | Mild | 06/12/94 | 10:52 | 06/12/94 | 1 | 18 | Poss. | None | Recovered | None |
| | M | LIGHTHEADEDNESS | Mild | 06/12/94 | 11:38 | 06/12/94 | | 32 | Prob. | None | Recovered | Other |
| (19) | F | VASOVAGAL EPISODE | Mild | 06/12/94 | 10:54 | 06/12/94 | | 53 | None | None | Recovered | Other |
| | F | VASOVAGAL EPISODE | Mild | 06/12/94 | 14:54 | 06/12/94 | | 58 | None | None | Recovered | Other |
| 21 | F | NAUSEA | Mild | 06/10/94 | 14:00 | 06/10/94 | 2 | 30 | Prob. | None | Recovered | None |
| TREATMENT GROUP: MS Gen 200mg | | | | | | | | | | | | |
| 10 | M | DROWSINESS | Mild | 06/12/94 | 10:30 | 06/14/94 | | | Prob. | None | Recovered | None |
| 11 | M | HEADACHE | Mild | 06/09/94 | 15:30 | 06/10/94 | 9 | 30 | Poss. | None | Recovered | None |
| | M | DROWSINESS | Mild | 06/12/94 | 10:15 | 06/13/94 | 20 | 50 | Prob. | None | Recovered | None |
| TREATMENT GROUP: Naltrexone HCL | | | | | | | | | | | | |
| (18) | M | HEADACHE | Mild | 06/08/94 | 13:45 | 06/08/94 | 3 | 45 | None | None | Recovered | None |
| 21 | F | TIREDNESS | Mild | 06/08/94 | 10:30 | 06/09/94 | 21 | 10 | None | None | Recovered | None |

PROTOCOL NO. M094-0309

TABLE 10C

SUMMARY OF THE MAXIMUM CONCENTRATION (CMAX) BY SUBJECT
MORPHINE
MSC 200MG AND MS GEN 200MG

Population: All Females Valid for Pharmacokinetic & Safety Analysis

INVESTIGATOR: 660

Cmax (ng/mL)

| Subject Number | Treatment | | Ratio (%) |
|---|---|---|---|
| | MS Gen 200mg | MSC 200mg | MS Gen 200mg / MSC 200mg |
| 2 | (b)(4)(CC) | | |
| 4 | | | |
| 5 | | | |
| 8 | | | |
| 13 | | | |
| 14 | | | |
| 16 | | | |
| 17 | | | |
| 19 | | | |
| 21 | | | |
| 22 | | | |
| N | 11 | 11 | 11 |
| Mean | 200.04 | 194.68 | 104.67(102.75)* |
| Std. Dev. | 47.16 | 44.79 | 19.90 |
| Geometric Mean | 195.07 | 189.80 | 102.78 |
| RSD % | 23.58 | 23.01 | 19.01 |

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* Value in parenthesis is the ratio of the treatment means.

CROSS REFERENCE:
Appendix: IV

PROTOCOL NO. M094-0309

TABLE 10B

SUMMARY OF THE MAXIMUM CONCENTRATION (CMAX) BY SUBJECT
MORPHINE
MSC 200MG AND MS GEN 200MG

Population: All Males Valid for Pharmacokinetic & Safety Analysis

INVESTIGATOR: 660

| | Cmax (ng/mL) | | |
|---|---|---|---|
| | Treatment | | Ratio (%) |
| Subject Number | MS Gen 200mg | MSC 200mg | MS Gen 200mg / MSC 200mg |
| 1 | (b)(4)(CC) | | |
| 6 | | | |
| 7 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 15 | | | |
| 18 | | | |
| 20 | | | |
| N | 10 | 10 | 10 |
| Mean | 179.39 | 177.17 | 103.28(101.25)* |
| Std. Dev. | 64.83 | 46.16 | 31.85 |
| Geometric Mean | 169.35 | 171.15 | 98.95 |
| RSD % | 36.14 | 26.05 | 30.84 |

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* Value in parenthesis is the ratio of the treatment means.

CROSS REFERENCE:
Appendix: IV